12/ Ext of time (2nd) + Appeal Brief (3)

PATENT
Attorney Docket No.: SALK1280-4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES

Bet 11-15-99

In re Application of:
Evans et al.

Application No.: 08/931,694

Filed: September 16, 1997

For: USE OF SELECTIVE LIGANDS FOR TREATMENT OF DISEASE STATES RESPONSIVE TO STEROID OR STEROID-LIKE HORMONES

Group Art Unit: 1614

Examiner: K. Jordan

CERTIFICATION UNDER 37 CFR § 1.8

I hereby certify that the documents referred to as enclosed herein are being deposited with the United States Postal Service as first class mail on this date 11/1/99, in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231

Stephen E. Reiter, Reg. No. 31,192
(Name of person mailing paper)

Signature 11/1/99
Date

Box AF
Assistant Commissioner of Patents
Washington, D.C. 20231

APPELLANTS' BRIEF UNDER 37 CFR 1.192

Sir:

INTRODUCTION

This is an appeal from a decision of the Examiner mailed December 31, 1998, finally rejecting pending claims 1, 5-8, and 16-18 in the above-identified patent application, which is a Divisional application of U.S. Serial No. 08/695,743, filed August 12, 1996, now issued as Patent No. 5,668,175 on September 16, 1997, which is a File Wrapper Continuation Application of U. S. Serial No. 08/193,146, filed February 14, 1994, now abandoned, which is a Continuation-in-Part application of U.S. Serial No. 07/748,767, now abandoned. Notice of Appeal was timely filed June 30, 1999. The Appeal Brief is being submitted in triplicate (an original and two copies) as required by 37 C.F.R. § 1.192(a).

REAL PARTY IN INTEREST

The real party in interest in this appeal is The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, California 92037.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

STATUS OF THE CLAIMS ON APPEAL

In the first Office Action mailed April 1, 1998, the Examiner rejected claims 1-15. In a Response mailed October 1, 1998, Appellants canceled claims 2-4 and 9-15 without prejudice, amended claim 1, and added new claims 16-18.

In the next Office Action dated December 31, 1998, the Examiner finally rejected claims 1, 5-8, and 16-18. In a Response mailed June 30, 1999, Appellants requested reconsideration of the pending claims.

Appellants timely filed a Notice of Appeal from the final rejection of claims 1, 5-8, and 16-18 on June 30, 1999.

In an Advisory Action mailed August 9, 1999, the Examiner maintained the rejections of record, and indicated that the request for reconsideration was considered, but did not place the Application in condition for allowance.

Accordingly, pending claims 1, 5-8, and 16-19, as they stand upon entry of the amendments in Appellant's Response mailed October 1, 1998, define the subject of this Appeal. A copy of pending claims 1, 5-8 and 16-19 is presented in Appendix A.

STATUS OF AMENDMENTS

Claim 1 remains as amended and claims 16-18 remain as presented in the Response mailed October 1, 1998. Claims 5-8 remain as presented at the time of filing in this Divisional Application. All claims depend from claim 1.

SUMMARY OF INVENTION

In accordance with the present invention, it has been discovered that there are compounds that selectively interact with a single steroid or steroid-like receptor subtype to a much greater extent than with other steroid receptor subtypes.[1] For example, retinoic acid has been discovered to have significantly different potency among various retinoid receptor subtypes. Thus, the rank order of potency of retinoic acid has been found to be RAR-γ $\angle$ RAR-β $\angle$ RAR-α $\angle$ RXR-α.[2] Such differentiation in compound activity between subtypes of steroid or steroids-like receptors is related to the fact that some classes of receptors include sub-types with distinctly different types of receptor.[3] Compounds that selectively interact with a single receptor subtype are useful for the treatment of steroid responsive disease states because they minimize the occurrence of side effects caused by the activation of hormone responsive pathways not directly associated with the disease state being treated.[4]

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[1] Specification, page 2, lines 32-35; page 4, lines 2-10; page 5, lines 10-26; and page 6, lines 1-5.

[2] Specification, page 11, lines 13-22.

[3] Specification, page 6, lines 7-20.

[4] Specification, page 5, lines 27-30

ISSUES

1. Are claims 1, 5-8, and 16-18 obvious under 35 U.S.C. § 103(a) over Crettaz et al. *Biochem. J.*, 272:391-397, 1990 (hereinafter "Crettaz"); Astrom et al. *BBRC,* 173(1):339-245, 1990 (hereinafter "Astrom"); EPA 0170105 (hereinafter "'105"); and EPA 0220118 (hereinafter "'118")?

GROUPING OF CLAIMS

Claims 1, 5-8, and 16-18 stand or fall together.

ARGUMENT

1. Claims 1, 5-8, and 16-18 are not obvious under 35 U.S.C. § 103(a) over Crettaz et al., Astrom et al.; EPA 0170105, and EPA 0220118.

The rejection of claims 1, 5-8, and 16-18 as allegedly being obvious under 35 U.S.C. § 103(a) over Crettaz et al., Astrom et al., '105, and '118 is submitted to be in error for the following reasons.

Appellants' invention is directed to methods for treating a disease state mediated by a particular steroid or steroid-like hormone receptor subtype in a subject in need thereof. The invention method, as defined by claim 1, distinguishes over the references relied upon, taken alone or in combination, by requiring the administration of an effective amount of a ligand that selectively interacts with the steroid or steroid-like hormone responsive receptor subtype associated with the disease state being treated, to a significantly greater extent than with other subtypes of the same receptor. Thus, the subject treated according to the invention method is one having a disease that is associated with a particular subtype of a member of the steroid/thyroid hormone superfamily of receptors. An important part of the invention method, therefore, involves selection of a ligand that will most efficaciously treat such a subject.

As acknowledged by the Examiner, the references cited "do not label the compounds as selective ligands" (Final Office Action, mailed December 31, 1998, page 2). In efforts to overcome this admitted deficiency in the references, the Examiner improperly advances the argument that an inherent mechanism of drug action would allegedly render the claimed treatment method obvious, as follows:

> ...pharmaceutical methods are not limited by the possible mechanism of drug action because all mechanisms inherently occur upon administration of the drug regardless of the label given to the compound.

(Final Office Action, page 2). The Examiner's improper reliance upon the inherent mechanism of drug action in framing the rejection is further illustrated in the Examiner's unsupported assertion that the compound of claim 16 would "inherently bind to certain receptor subtypes in a selective manner when the compound is administered to patients with skin disorders and cancer as was performed in the Crettaz reference" (Final Office Action, page 2). Appellants submit that this line of argument is improper under 35 U.S.C. § 103.

According to ***In re Spormann,*** a rejection for alleged obviousness is <u>not</u> properly based upon inherency:

> [The] inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.

150 *USPQ* 449, 452 (C.C.P.A. 1966). Consistent with Spormann, Appellants submit that the *prima facie* obviousness of Appellants' method claims is not established by the Examiner's unsupported assertion that particular compounds disclosed by Crettaz, or any of the other references cited herein, would inherently bind with specificity to a particular receptor subtype. Appellants' invention is based upon the discovery that ligands exist that can select between otherwise very closely related members of the steroid/thyroid hormone superfamily of receptors. All pending claims require administration of a ligand that selectively interacts with the receptor subtype associated with a steroid or steroid-like hormone responsive disease state, to a

significantly greater extent than with other subtypes of the same receptor class. Thus, administration of such a compound to a subject having a disease state associated with the receptor with which the compound selectively interacts affords particular therapeutic advantage, for example by minimizing the occurrence of side effects caused by the activation of hormone responsive pathways not directly associated with the disease state being treated.

Further, Appellants respectfully disagree with the Examiner's assertion (with respect to the compound of claim 16) that Crettaz teaches "the use of such compounds to treat retinoid responsive skin disorders and cancer (page 391, column 1, first paragraph)" (Final Office Action, page 2). Appellants respectfully submit that Crettaz fails to teach or suggest that specific disease states are responsive to treatment by retinoids that bind with specificity to a particular retinoid receptor subtype, or that unwanted side effects of retinoid treatment can be minimized by selecting a ligand having selective activity that is matched to the cellular mechanism operative in the particular disease state being treated. In fact, Crettaz's statement regarding the therapeutic utility of retinoids (relied upon by the Examiner) refers to synthetic retinoids as a single "class of compounds" having value in the treatment of such various diseases as "dermatological disorders" and "cancer" (Crettaz, page 391, column 1, first paragraph). Clearly, there is no recognition in Crettaz that different receptor subtypes are involved in the various diseases referred to, much less any suggestion that compounds showing a difference in specificity between receptor subtypes would have utility in the treatment of a subject having a disease state associated with a particular receptor subtype. Thus, Crettaz fails to suggest the invention of claim 1 precisely because Crettaz fails to teach or suggest selecting a receptor-subtype specific ligand to use in treatment of a subject having a disease state associated with a particular subtype of a member of the steroid/thyroid hormone superfamily of receptors.

Further reliance on Astrom does not cure the deficiencies of Crettaz. Appellants respectfully disagree with the Examiner's assertion that:

> Astrom teaches compound II, etretin (page 340, "Materials") may be useful as an antitumor and antipsoriatic agent ...

(Final Office Action, page 2). Astrom's comment regarding efficacy of "retinoids" speaks only in general terms about the efficacy of "retinoids" as a class (Astrom, page 339, first paragraph) and does not identify any diseases associated with any particular receptor subtype. Indeed, Astrom does not even distinguish between the classes of RAR and RXR. Thus, Astrom fails to suggest Appellants' method of treating subjects having a disease associated with a particular retinoid receptor subtype by administration of a retinoid compound that selectively binds to a particular RAR or RXR receptor subtype.

Further reliance on EPA '105 is unable to cure the deficiencies of Crettaz and Astrom, as EPA '105 also fails to disclose or suggest the use of compounds that have the ability to selectively interact with one specific steroid or steroid-like hormone-responsive receptor subtype relative to other subtypes of the same class for the treatment of disease states associated with that particular receptor subtype. Contrary to the Examiner's assertion that "105 teaches retinoids for treating leukemia specifically ... and compounds encompassing applicant's compound III for treating malignant diseases" (Office Action mailed April 1, 1998, page 4), '105 fails to disclose which of the many benzoic acid derivatives disclosed therein would be chosen to treat a subject afflicted with mylogenous leukemia or any of the other disorders mentioned therein. Moreover, EPA '105 fails to suggest that the most efficacious way to treat a disease state associated with a particular steroid or steroid-like responsive receptor subtype is to select a ligand that selectively interacts with that particular receptor subtype. Thus, EPA '105 fails to suggest treatment of a disease state associated with a particular steroid or steroid-like responsive receptor subtype by selection of a ligand that selectively interacts with that particular receptor subtype, as required by Appellants' claim 1.

Further reliance on EPA '118 is unable to cure the deficiencies of Crettaz, Astrom, and EPA '105. Similar to the other three references relied on, EPA '118 does not disclose or suggest the use of compounds that have the ability to selectively interact with one specific steroid or steroid-like responsive receptor subtype (e.g., RARα v RARβ), relative to other retinoid responsive receptor subtypes, to treat a subject having a disease state associated with a particular receptor subtype.

As neither Crettaz, Astrom, EPA '105, nor EPA '118 discloses or suggests the use of ligands that are selective for specific steroid or steroid-like hormone-responsive receptor subtypes in a patient having a disease state associated with such a particular steroid or steroid-like responsive receptor subtype, the combination of references relied upon does not disclose or suggest Applicants' claimed method. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

In view of the above, Appellants respectfully submit that claims 1, 5-8, and 16-18 are not obvious under 35 U.S.C. § 103.

APPENDIX

Appendix A contains a copy of pending claims 1, 5-8, and 16-18 that are the subject of the present appeal.

CONCLUSION

In view of the above remarks, it is respectfully submitted that claims 1, 5-8, and 16-18 are in condition for allowance. Accordingly, it is respectfully submitted that the decision of the Examiner, finally rejecting claims 1, 5-8 and 16-18, should be reversed.

Respectfully submitted,

Date: 11/1/99

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Enclosure: Appendix A

APPENDIX A

PENDING CLAIMS—U.S. Serial No. 08/921,694

1. A method for the treatment of a steroid or steroid-like hormone-responsive disease state in a subject in need thereof, said method comprising administering to said subject an effective amount of a ligand which selectively interacts with the receptor subtype associated with said steroid or steroid-like hormone responsive disease state, to a significantly greater extent than with other subtypes of the same receptor class.

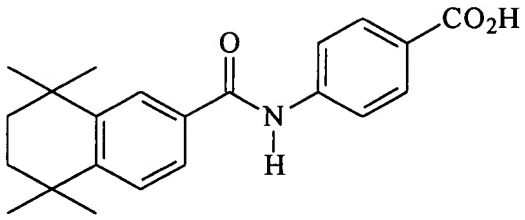
5. A method according to Claim 1 wherein said steroid or steroid-like hormone responsive disease state is the result of translocation of a portion of a gene encoding a member of the steroid/thyroid superfamily of receptors and a portion of a second gene; wherein the expression of said second gene is not ordinarily subject to regulation by the steroid or steroid-like hormone which binds to said member of the steroid/thyroid superfamily of receptors.

6. A method according to Claim 5 wherein said steroid or steroid-like hormone-responsive disease state is APL.

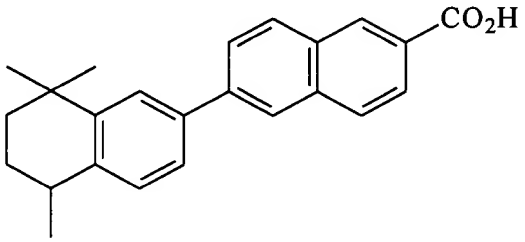
7. A method according to Claim 1 wherein said steroid or steroid-like hormone-responsive disease state is a skin disorder.

8. A method according to Claim 1 wherein said ligand which selectively interacts with the receptor subtype associated with said steroid or steroid-like hormone responsive disease state is selected from RAR-α selective ligands, RAR-ß selective ligands, RAR-γ selective ligands, TR-α-selective ligands, TR-ß-selective ligands, RXR-α selective ligands, RXR-ß selective ligands, RXR-γ selective ligands, coup-α selective ligands, coup-ß selective ligands, or coup-γ selective ligands.

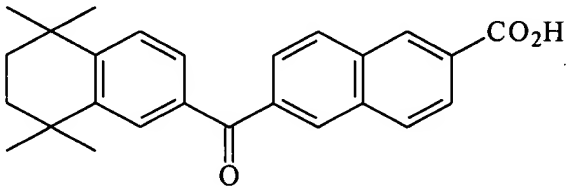
16. A method according to Claim 8 wherein said RAR-α selective ligand is the amide:



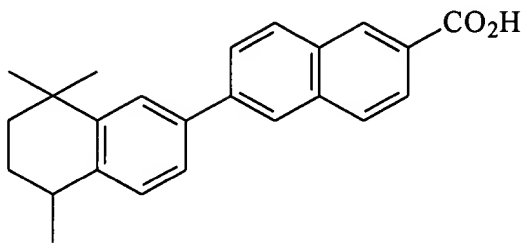
17. A method according to Claim 8 wherein said RAR-ß selective ligand is the phenyl-naphthyl derivative:



or benzophenone derivative:



18. A method according to Claim 8 wherein said RAR-γ selective ligand is the phenyl-naphthyl derivative:



or benzophenone derivative: